CLINICAL REVIEW OF BLA REFERENCE NO. BLA 97-0260 AND BLA 97-0244

BLA reference # BLA 97-0260 (IDEC) and BLA 97-0244 (Genentech)

Product:

- licensed name - rituximab recombinant
- trade name - Rituxan™

Sponsors:

Manufactured by:	Manufactured and Distributed by:
IDEC Pharmaceuticals Corporation 11011 Torreyana Road San Diego, CA 92121	Genentech, Inc. 460 Point San Bruno Blvd. South San Francisco, CA 94080-4990

CLINICAL REVIEWER: BERNARD W. PARKER, M.D.

11/24

Ken Davis 11/25/97

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Proposed indication: Rituximab is indicated for treatment of patients with relapsed or refractory lowgrade or follicular B-cell non-Hodgkin's lymphoma (indolent lymphoma).

II. Background (synopsis of the data contained in the original BLA #)

Description

(b)(4) Rituximab is a genetically engineered [~~~] monoclonal antibody [~~~] IgG_1 kappa immunoglobulin; [~~~] containing [~~~] light- and heavy-chain variable region sequences (Fab domain) and [~~~] constant region sequences (Fc domain). Rituximab binds specifically (high binding affinity of 5.2 to 11.0 nM) to the antigen CD20, a transmembrane differentiation antigen (Bp35) located only on pre-B and mature B-lymphocytes.

Clinical Pharmacology

In patients treated with either 125, 250 or 375 mg/m^2 Rituximab given as an intravenous infusion once weekly for 4 doses, serum antibody concentrations increased with increasing doses. In those patients receiving the 375 mg/m^2 Rituximab dosage, the following parameters were noted:

	Post-1st Infusion	Post-4th Infusion
mean $t_{½}\beta$	68.1 hr	189.9 hr
mean C_{max}	238.7 µg/ml	480.7 µg/ml
mean Cl_{plasma}	0.0459 l/hr	0.0145 l/hr

(There is no mention of how Rituximab is cleared; it might be cleared the same as other antibodies -- namely via hepatically and through the reticuloendothelial system.)

Rituximab serum concentrations were significantly higher for responders compared with non-responders. This difference reached statistical significance prior to the 2nd and 4th infusion, after the 4th infusion, at one week, and one and 3 months ($p \leq 0.009$). Typically, rituximab was detectable for 3-6 months following completion of treatment.

A marked decline in median B-cell counts was noted in blood after the 1st dose of Rituximab. B-cell recovery began at @ 6 months following the completion of treatment. B-cell levels returned to normal between 9-12 months after completing the treatment.

Clinical experience:
There is no previous clinical experience with Rituximab outside of these clinical studies.

Data derived from two studies (pivotal Phase III controlled study 102-05 and supportive Phase I/II study 102-02, Phase II part) provide the main evidence of clinical efficacy for the claimed indication. All patients (total of 203 patients) enrolled in both the pivotal study (166) and the supportive study (37) had progressive disease where observation alone ("watch and wait") would not be justifiable.
Below is the list of IDEC-C2B8 (rituximab; Rituxan™) protocols, with safety and efficacy data (from an intent-to-treat population) reported as of November 1996.

Study	Type	Description	Status	Patient Safety/ Efficacy	Indication	Dose Range	Frequency of IDEC-C2B8 Dosing
102-01	Phase I/II Uncontrolled Open-label	Single-Dose, Single-Agent	Completed	15/15	All types of relapsed B-cell lymphoma	10 - 500 mg/m^2	Single dose
102-02	Phase I/II Supportive Open-label	Multiple-Dose, Single-Agent	Completed	47/47	All types of relapsed B-cell lymphoma	125 - 375 mg/m^2	1/week for 4 doses
102-03	Phase II Uncontrolled Open-label	Multiple-Dose Combined with CHOP	Completed	40/40	Low-grade or follicular (chemo-naive) B-cell lymphoma	375 mg/m^2	6 doses administered on day 1, 6, 48, 90, 134, 141
102-04	This study was planned but never implemented.						
102-05	Phase III Controlled Open label	Multiple-Dose, Single-Agent	Completed	166/166	Relapsed Low-grade or Follicular B-cell lymphoma	375 mg/m^2	1/week for 4 doses
102-06	Phase II Uncontrolled Open-label	Multiple-Dose, Single-Agent	Accrual Completed but Follow-up Ongoing	32/20	Relapsed Low-grade or Follicular B-cell lymphoma	375 mg/m^2	1/week for 8 doses
102-07	Phase II Uncontrolled Open-label	Multiple-Dose Combined with Interferon-α	Ongoing	0/0	Relapsed Low-grade or Follicular B-cell lymphoma	375 mg/m^2	1/week for 4 doses
102-08	Phase II Uncontrolled Open-label	Multiple-Dose, Single-Agent	Ongoing	Bulky disease 13/10; Retreatment 9/8	Relapsed Low-grade or Follicular B-cell lymphoma	375 mg/m^2	1/week for 4 doses
Total	322/306						

III. Information on NHL (particularly the indolent lymphomas) and "natural history" of low-grade NHL

Non-Hodgkin's lymphomas (NHL) comprise a group of neoplasms of the lymphoid system; it is the 6th most common cause of cancer-related deaths in the U.S.A. Presently there are @ 40,000 new cases annually in the United States, with the incidence rising dramatically (cannot be totally explained by the AIDS epidemic). Only lung, breast, prostate, colo-rectal and bladder cancers exceed NHL in annual incidence. NHL's are more than five times as common as Hodgkin's disease; 85% are of B-cell origin. The following table (source: Rosenberg, S.A., et al. Cancer 49: 2112, 1982) is the Working Formulation classification of NHL.

Grade	Type	Malignant Lymphoma type	Frequency (%)*	Median age (yrs)	Stage III/IV (%)	Marrow involved (%)	Median survival (yrs)	5-year survival (%)
Low	A	Small lymphocytic • CLL-type • Plasmacytoid	3.6	60	89	71	5.0	59
	B	Follicular, small cleaved cell	22.5	54	82	51	7.2	70
	C	Follicular, mixed (small cleaved and large cell)	7.7	56	73	30	5.1	50
Intermediate	D	Follicular, large cell	3.8	55	73	34	3.0	45
	E	Diffuse, small cleaved cell	6.9	58	72	32	3.4	33
	F	Diffuse, mixed cell (small and large cell)	6.7	58	55	14	2.7	38
	G	Diffuse, large cell	19.7	57	54	10	1.5	35
High	H	Immunoblastic (large cell)	7.9	51	49	12	1.3	32
	I	Lymphoblastic	4.2	17	73	50	2.0	26
	J	Small, non-cleaved • Burkitt's • Non-Burkitt's	5.0	30	66	14	0.7	23

*The total is 88.0%, for the Working Formulation does not include cutaneous T-cell lymphomas, adult T-cell leukemia-lymphoma, diffuse-intermediately differentiated lymphocytic lymphoma and malignant histiocytosis, which constitute 12% of cases.

Based on the table above, most adults with NHL's have either collectively the indolent follicular lymphomas (consisting of follicular small cleaved-cell, follicular mixed, and follicular large cell; 35%) or collectively the aggressive diffuse large B-cell lymphoma (consisting of diffuse large cell and immunoblastic types; 30%).

Survival differs between the lymphomas based on the grade; although low-grade NHL have a higher percentage of survivors at 5 years, such slow-growing tumors are much less curable than the intermediate and high grade NHL's. The low-grade lymphomas have a high percentage of advanced stage at presentation and are rarely curable; this holds true even if such patients were diagnosed at an earlier stage. On the other hand, the intermediate and high-grade lymphomas have a higher number of earlier staged disease (Stages I and II) at 30-40% and are highly (80-90%) curable. Additionally, 30-40% of patientts with Stage III and IV intermediate and high grade NHL are curable with differing combinations of cytotoxic therapy available today.

Among the indolent lymphomas, the follicular lymphomas are the most common (in the Western hemisphere), constituting @ 45% of all NHL's and 80% of all indolent lympomas. Approximately 80% to 90% of these patients (exclusively in adults) present with advanced stage disease (Stage III-IV). A unique characteristic of this lymphoma, as well as all the low-grade lymphomas, is the phenomenon of ***spontaneous regression. Spontaneous regression***, although noted to occur in up to 30% of patients in one series, is usually partial and typically short-lived (1-2 years).

An additional event that ultimately occurs in patients with low-grade NHL's is the transformation from a low-grade to a high-grade lymphoma; such a transformation has a poor prognosis, with survival lasting less than a year. This event may occur due to genetic changes, being either

(a) a loss of p53 (17p mutation) $\rightarrow \uparrow$ cyclin-dependent kinase type 4 $\rightarrow$ phosphorylation of Rb and E2F release, or

(b) the presence of t(14;18) $\rightarrow$ overexpression of BCL-2.

The time for this transformation varies between 8 months and 25 years (no plateau; high degree of heterogeneity), whti 40% to 70% transformed at 8-10 years of follow-up. Prognostic factors at the time of transformation include (a) the bulk of the disease ($\geq$ 10 cm. in the largest diameter) and (b) the response to the chemotherapy. Treatment at this point would be intensive multi-therapy chemotherapy regimen or a non-cross-resistant regimen.

Prognostic factors include the following for low-grade lymphomas:

(1) The greater the sensitivity to therapy, thereby leading to complete response (CR) or an "excellent" partial response (PR), the better the prognosis.

The response criteria are as follows:

- **CR** (complete response) = no clinical, radiological, or other evidence of disease.
- **PR** (partial response) = $\geq$ 50% $\downarrow$ in the sum of the products of the largest diameters of ***all*** measurable disease.
- **PD** (progressive disease) = $\geq$ 25% $\uparrow$ in size of at least one measurable disease/lesion.
- **CRu** (unconfirmed/uncertain) = a new class indicating radiological abnormalities at the site of previous disease, not consistent with previous responses with the therapy. (This in the past would be construed by the investigators to include such responses under "CR" or "PR"; such responses will be less now.)

(2) Patients diagnosed with localized (Stage I or II) disease have a better prognosis.

[This type /grade of NHL is radiation-sensitive and are treated with radiation therapy; however, at advanced stages, radiation + systemic chemotherapy leads to conflicting results, without any survival advantage over only systemic chemotherapy.]

(3) Patients diagnosed with follicular mixed (small cleaved and large cell) lymphomas are rarely curable with some adriamycin-based and other chemotherapeutic regimens.

(4) Additional unfavorable prognostic factors that are independently significant are:

- extent of bone marrow involvement (> 20% involvement; reflects tumor growth)
- bulky disease (> 5 cm., reflecting tumor growth)
- more than one extranodal site (associated with survival in all patients)
- LDH >1x normal values (especially for patients $\leq$ 60 years old; survival association)
- elevated β_2-microglobulin (reflects tumor growth)
- poor performance status (especially for patients $\leq$ 60 years old; survival association)

[NOTE: Follicular lymphomas are noted to have the t(14;18) genetic defect, in which there is overexpression of the BCL-2 gene, which blocks apoptosis. This is not listed as an unfavorable prognostic factor because its presence does not have an impact on survival; it may indicate chemo-resistance.]

(5) Younger and older patients have significantly different outcomes; patients < 60 years of age with the unfavorable clinical features are more likely to be candidates for intensive experimental regimens. Patients at 60 years of age and older are more often observed closely without therapy until the need for palliative single-agent oral therapy.

(6) A powerful predictor of survival is initial response to therapy. Greater than 80% complete responders are alive at 7 years (compared with the median survival of 2 years for ***all*** patients with low-grade NHL).

Clinical characteristics	Independent risk factors associated with the characteristics
Growth/Invasive potential of the tumor	LDH, stage, tumor size, # nodal/extranodal site, bone marrow involvement, β_2-microglobulin
Patient's response to tumor	Performance status, B-symptoms
Patient's ability to tolerate intensive therapy	Performance status, age, bone marrow involvement

Therapy for indolent (low-grade) lymphomas at the later stages (Stage III or IV) are listed below. Overall response rates with different chemotherapeutic regimens are between 80% to 90%, with CR's occuring between 23% to 83% in various studies. Unfortunately, the responses last only a median of 2 years and in many studies, < 10% of patients remain in remission for more than 5 years. Despite the lack of duration, median survival is > 9 years in many series. The choice for either (a) a conservative approach or (b) an aggressive approach exists because there is still no evidence that one is more effective than the other in terms of overall survival. **Of note, despite the aggressive treatment modalities' CR rates being > 50%, subsequent relapses occur at a rate of approximately 10-15% per year, regardless of therapy. At relapse, favorable predictors for survival include (1) having a CR in the initial therapy, (2) the first response lasting for ≥ 12 months, and (3) the patient's age < 60 years old.** Below are the treatment options:

CONSERVATIVE THERAPY

(1) No therapy -- the majority of patients may simply be observed until onset of symptoms or rapid nodal growth. The median times of observation varies from 16 months (for follicular mixed NHL) to 72 months or more for the more indolent small lymphocytic group. ***Spontaneous remissions may occur during the observation period.*** The advantage of this approach is the avoidance of side effects of early treatment , but the disadvantages are the continuous growth of disease (constantly there to remind the patient of disease) and lower rates of CR when treated later in disease (? due to an ↑ in chemo-resistance genes such as BCL-2 overexpression). Patients at 60 years of age and older are more often observed closely without therapy until the need for single-agent oral therapy.

(2) Single agent therapy with chlorambucil or cyclophosphamide gives good responses (CR or excellent PR in 60-80% of patients) for these NHL's. Patients treated with single-agent therapy after a period of "watch-and-wait" have response rates between 30% to 60% with a median response duration of only 18-24 months. However, adverse effects include myelosuppression and, in the case of cyclophosphamide, hemorrhagic cystitis. Other single agents include the purine analogues fludarabine and 2-chlorodeoxyadenosine (2-CdA) which may lead to a 40-50% response rate.

AGGRESSIVE THERAPY

(3) Combination chemotherapy, like single-agent chemotherapy, produces CR's or excellent PR's in 60-80% of patients. The only advantage of combination chemotherapy over single-agent chemotherapy is the rapid response obtained. Both modalities of chemotherapy are given until a maximum response is achieved, but not as "maintenance" therapy (which would be potentially leukemogenic and compromise further treatment, as well as not having a survival advantage). Commonly used regimens include CHOP (cyclophosphamide, adriamycin, vincristine, and prednisone), CVP (cyclophosphamide, vincristine and prednisone), and C-MOPP (cyclophosphamide, mechlorethamine, vincristine, procarbazine, and prednisone). Patients who relapse after ≥ **12 months of a CR/PR** may be **retreated** with the same treatment previously given.

> {NOTE: For ***relapsed*** low-grade NHL's, synergism between ARA-C and CDDP led to the development of the ESHAP combination [consisting of etoposide (E); methylprednisolone, a.k.a. Solu-Medrol (S); high-dose ARA-C (HA); and cisplatin (P)]. The CR rate after using this regimen is 35% and the PR rate is 40%.}

NEW ACTIVE AGENTS

(4) Interferon-alpha (IFN-α) has activity; its role in routine management of low-grade NHL's is for patients whose disease does not respond to conventional chemotherapy. The effect of IFN-α on survival is presently unknown; its

response rate (as a single agent) is 40-60% of patients (CR rate of 10%) with doses as low as 2 million units three times weekly. Toxicity include flu-like symptoms, capillary-leak syndrome, and neurologic toxicities. ECOG performed a trial, comparing COPA (modified CVP regimen) alone versus COPA + IFN-α and found that the latter regimen led to fewer patients having progressive disease at 5 years (66% vs. 81%) but no difference in overall survival.

(5) Nucleoside analogues such as 2' deoxycoformycin (pentastatin or DCF, which inhibits adenosine deaminase), fludarabine (derivative of cytosine arabinoside) and 2-chlorodeoxyadenosine (2-CdA, fludarabine analogue which also inhibits adenosine deaminase) have activity against indolent lymphomas. Their distinct effectiveness in indolent lymphomas (not noted in aggressive lymphomas) is their ability to induce apoptosis. The response rate is up to 40-50% in previously treated low-grade lymphoma patients. Therapy with 2-CdA, in one study, led to a 35% CR rate and 54% PR rate, with a median response duration of 10 months. Therapy with fludarabine led to an overall response rate of 37%, with 62% being follicular small cleaved cell-type, 80% being of follicular mixed type, and 100% of follicular large-cell type. In another study, patients with previously untreated disease had an overall response rate of 65%, a CR rate of 37%, and a median progression-free survival of 13.6 months.

EXPERIMENTAL BIOLOGICAL THERAPY

(6) Bone marrow transplantation (BMT) with high-dose chemotherapy has been reserved for the younger patients (< 60 years of age) who failed previous therapy; such patients have usually undergone 2 or subsequent remissions. However, $\geq$ 50% ultimately relapse after therapy with BMT. The therapy consists of two components:

I. Preparatory regimen of (a) fractionated total body irradiation and (b) high-dose cyclophosphamide.

II. Autologous bone marrow rescue -- the marrow is purged with monoclonal antibodies and rabbit complement.

The result is a 33% relapse at follow-up at 3.5 years (consistent with a 30-45% relapse with chemotherapy) only amongst those patients in their 2nd remission. Other types of transplantation includes the use of (a) autologous peripheral blood stem cells, which would theoretically lead to less contamination with tumor cells than autologous BMT, and (b) allogeneic BMT, which may have a better response rate due to the graft-vs.-lymphoma cells effect. However, with the allogeneic BMT, there is an increase in morbidity and mortality due to the graft-vs.-host disease effect.

(7) Monoclonal antibodies of several types are being studied. Anti-idiotype antibodies, generated against the patient's own lymphoma idiotype, and idiotype vaccines that lead to occasional durable responses. The vaccines produce a polyclonal antibody response against the idiotype, thus circumventing the problems with somatic mutations observed in the idiotypes of this disease.

Monoclonal antibodies to common lymphoma antigens are also being studied. In this case, an antibody directed against CD20, a B-lymphocyte differentiation antigen, produced by IDEC Pharmaceutical Corporation , has demonstrated efficacy in patients with low-grade NHL's.

SYNOPSIS #1 (Protocol 102-02)

INVESTIGATORS: The study was conducted at seven sites in the United States. The project clinician at IDEC Pharmaceuticals was Antonio J. Grillo-López, M.D.

OBJECTIVES:
1) Identify a biologically active tolerated dose (BATD) and dose-limiting toxicities (DLTs) for efficacy trials of IDEC-C2B8 given weekly as single intravenous infusions times four in patients with relapsed B-cell lymphoma,
2) Characterize the safety and toxicity profile of IDEC-C2B8, including qualitative and quantitative toxicities, and define their duration and reversibility,
3) Monitor for tumor penetration, IDEC-C2B8 serum levels, human anti-mouse antibody (HAMA), and human anti-chimeric antibody (HACA) levels,
4) Evaluate the pharmacokinetics of intravenous IDEC-C2B8 and
5) Evaluate clinical activity and determine Phase II response rate.

STUDY DESIGN: An open-label, single-arm, multi-center Phase I (dose escalation) and Phase II (clinical activity) study was conducted in which each patient received a single intravenous IDEC-C2B8 infusion (125, 250, or 375 mg/m^2) weekly for a total of four infusions.

PATIENT POPULATION: Patients with recurrent histologically confirmed B-cell lymphoma of any grade with measurable progressive disease were eligible, as were nonresponders to first chemotherapy or immunotherapy.
Tumors were required to be CD20+, and patients were to have a normal hematological status within seven days prior to initial therapy. Low-grade lymphoma patients were to have relapsed after one to four prior standard therapies. Intermediate- or high-grade patients were to have relapsed after one to three prior therapies.

STUDY TREATMENT: The chimeric mouse/human anti-CD20 monoclonal antibody IDEC-C2B8 was given as a single intravenous infusion at a maximum rate of 150 mg/ hour on a once weekly schedule for four infusions.
The first dose level was 125 mg/m^2 (3 patients), the second 250 mg/m^2 (seven patients), and the third 375 mg/m^2 (37 patients).

PATIENT CHARACTERISTICS AND DISPOSITION: Phase I patients (# 1-20) received 125, 250, or 375 mg/m^2; Phase II included 37 patients (#11 - 47) who received 375 mg/m^2. Thus, patients 11-20 are reported for Phase I and II.

Phase I characteristics included median age of 59 years (range 29 - 81 yr), 50% female, 90% Caucasian, low-, intermediate-, and high-grade histologies, and 85% stage III/IV at initial diagnosis. Phase II demographics included median age of 58 years (range 29 - 81 yr), 43% female, 95% Caucasian, 95% low-grade and follicular histology, and 76% stage III/IV at initial diagnosis.

At Phase II initiation, enrollment was restricted to low-grade or follicular histologies. Thus, Phase I/II patient 012 with intermediate-grade histology (Class G) was not evaluable.

Three patients discontinued prematurely due to adverse events: patient 009 with an elevated bilirubin thought related to viral hepatitis; patient 015 with Grade 4 thrombocytopenia and Grade 3 anemia, and patient 028 with a myocardial infarction five days after first infusion. Overall, 44 of 47 patients received all four infusions and completed followup.

Characteristics for Protocol 102-02: Combined Phase II Efficacy Population (37 Patients treated at 375 mg/m^2 dose)	
Variable	Results
Age (years) Median Range	 58 29 - 81
Gender Female Male	 16 (43%) 21 (57%)
Race Caucasian Black Asian	 35 1 1
Low Grade [IWF] (n=34) A B C	 4 21 9
Intermediate Grade* (n=3) D G	 2 1

The intent-to-treat population was utilized for all safety analyses and the efficacy population was utilized for all efficacy analyses. The number of subjects in each category and reasons for exclusion of subjects from the "efficacy" subpopulation are provided below.

Protocol 102-02: Patient Populations				
Phase	**Patient No.**	**Entered**	**Evaluable for**	
			Safety	**Efficacy**
I	1 - 20	20	20	18
I I	11 - 47	37	37	34

The following patients were considered not evaluable for efficacy:

- Patient 009 received one infusion; treatment was discontinued for hyperbilirubinemia attributed to viral hepatitis
- Patient 015 received one infusion; treatment discontinued for grade 4 thrombocytopenia and grade 3 anemia
- Patient 028 received one infusion; treatment was discontinued for myocardial infarction on study day 5

- Patient 012 did not have low-grade or follicular NHL but IWF G.

The following additional subjects with protocol violations were considered by the sponsor to be evaluable:

- Patient 011 did not undergo a repeat bone marrow biopsy within 30 days of treatment as required by protocol; previous biopsies were negative for lymphomatous involvement
- Patient 006 had a myocardial infarction (MI) four months prior to enrollment; the protocol excluded patients who experienced a MI within six months of study enrollment.
- Patient 041 had a previous malignancy (cutaneous melanoma) but had been disease-free for 14 years prior to study enrollment.
- Patient 046 had a baseline WBC count of 2840/mm^3 that was slightly under the required minimum of 3000/mm^3.

EFFICACY: In Phase I, 6 of 18 evaluable patients (33%) had a partial response (PR). In Phase II, complete responses (CR) were noted in 3 of 34 evaluable patients (9%) and partial responses in 14 of 34 evaluable patients (41%) for an overall response rate of 50% in evaluable patients (17/34). The median time to onset of response in responders was 50 days (range of 7 - 112 days). The median duration of response after treatment with IDEC-C2B8 was 8.6 months (2.6 - 26.2+) for the 17 responders in Phase II. The median duration of response to last chemotherapy prior to IDEC-C2B8 treatment was 12 months and to last therapy was 9.5 months for the same 17 patients. There is no statistically significant difference between these durations of response. When the 17 responders to IDEC-C2B8 are compared with all responders to last chemotherapy or to last therapy, there is no statistically significant difference in the duration of response ($p = .54$ and .64, respectively). The median time to progression for responders was 10.2 months (4.2 - 27.9+). Time to progression has exceeded 20 months in five patients at the time of the original BLA submission, with three still in remission at 24.8, 27.0, and 27.9 months.

SAFETY: Adverse events were most frequently infusion-related and included Grade 1 or 2 fever (85% Phase I patients; 73% Phase II patients), asthenia (45%;16%), chills (45%; 38%), nausea (25%;19%), vomiting (20%; 11%), rash (10%; 14%), and tumor site pain (10%; 3%).

Hypotension occurred in six patients (5%; 16%) and was Grade 1 (not requiring therapy) in three and Grade 2 (not requiring hospitalization) in three. Infusion-related adverse events resolved completely, usually within hours, and the incidence of infusion-related events decreased dramatically after the first infusion. No relationship was seen between dose levels or cumulative dose and toxicity.

Hematologic toxicity was usually mild and reversible. WBC toxicity grading increased by one grade in 30% of patients, by two grades in 15% and by three grades in 6%. Absolute granulocyte count (AGC) toxicity grading increased by one grade in 27% and by two grades in 3%. Three patients (8%) developed a four-grade increase in toxicity grading for AGC. One of these, who had a circulating malignant lymphocyte clone of >50,000/mm^3, had a reduction in AGC to 500/mm^3 on day 1 but recovered on day 8. The other two developed late-onset Grade 4 neutropenia at four and ten months, respectively, that was attributed to an unknown cause, was transient and resolved. Toxicity grading for platelet counts increased by one grade in 15%, by two grades in 2% and by 3 grades in 2% (1 patient). The latter patient developed thrombocytopenia and anemia that responded to steroids. Toxicity grading for hemoglobin values increased by one grade in 38% of patients, by two grades in 2% and by three grades in 2%. Only three patients developed trilineage effects.

Seventeen infections, reported in 14 of 47 patients (30%), were Grade 1 or 2 except for one Grade 3 herpes simplex infection. No clinically significant renal or hepatic toxicity was noted. Mean serum immunoglobulin levels remained stable, although some patients experienced transient reductions which recovered to baseline levels by the 20^{th} - 50^{th} study day. One patient developed a detectable, but not quantifiable HACA seven months posttreatment; no HAMA response was noted. Three deaths during followup (2.5 to 4.3 months following last infusion) were not judged as related; two were disease-related and one was due to secondary malignancy.

Incidence of Most Frequent Adverse Events by Dosing Group in Phase I (N= 20)			
Any Adverse Event	**Dosing Group (mg/m^2)**		
	125 (N = 3)	250 (N = 7)	375 (N =10)
Body As A Whole	N = 3	N = 7	N = 9
Fever	3	6	8
Vasodilation	0	0	1
Chills	2	5	2
Digestive System			
Nausea	2	1	2
Vomiting	1	1	2
Hematopoietic and Lymphatic System			
Thrombocytopenia	0	0	3
Coagulation Disorder	0	0	2
Skin and Appendages			
Pruritis	0	1	1
Rash	0	0	2
Urticaria	1	0	1

Overall toxicity was mild to moderate. Adverse events were primarily infusion-related and included Grade 1 or 2 fever in approximately three-quarters of the patients, chills and asthenia in approximately 40%, nausea and emesis in 10-20%, and rash in 10-14%. Hypotension occurred in six patients (13%) and was Grade 1 in three and Grade 2 in three. Infusion-related adverse events resolved, usually within hours, and the incidence of infusion-related events decreased after the first infusion (see the next table, Integrated Safety Summary).

The most common laboratory abnormalities observed were mild to moderate hematologic dysfunction, particularly lymphocytopenia and neutropenia. Thirty percent grade 1, 15% grade 2, and 6% grade 3 leukopenia and 27% grade 1, 3% grade 2, and 8% (3 patients) with grade 4 neutropenia were reported. Two of the subjects with grade 4 neutropenia developed this as a late toxicity (at 4 and 10 months, respectively) and these events resolved. The third subject was reported to have grade 4 neutropenia on study day 1 which had improved by study day 8. Fifteen percent of patients were reported to have grade 1, 2% with grade 2, and 2% (one patient) with grade 4 thrombocytopenia (the latter responded to steroid therapy). Grade 3 anemia was reported in 2% (1 patient). Three of the patients had more than one lineage affected. The toxicity profile for the 37 patients treated at 375 mgm^2 are presented in tabular form.

Seventeen infections were reported in 14 of the 47 patients (30%). This included one Grade 3 herpes simplex infection. Mean serum immunoglobulin levels remained stable, although some patients experienced transient reductions which recovered to baseline levels by study days 20 - 50.

One patient developed a detectable, but not quantifiable HACA seven months post-treatment; no HAMA response was noted.

Three deaths during followup (2.5 to 4.3 months following last infusion) were not judged by the clinical investigator at unrelated to study drug. In two patients, death was due to disease-progression and in one patient, death was ascribed to a secondary malignancy.

Protocol 102-02 Incidence of Adverse Events by Grade and by Patient @ 375 mg/m^2 dose (N = 37)				
Any Adverse Event	**Grade I** N = 10	**Grade II** N = 18	**Grade III** N = 2	**Grade IV** N = 2
Body As A Whole				
Fever	16	11	0	0
Chills	8	6	0	0
Headache	6	0	0	0
Cardiovascular System				
Hypotension	3	3	0	0
Digestive System				
Nausea	7	0	0	0
Vomiting	2	2	0	0
Abdominal Pain	0	0	1	0
Hematopoietic and Lymphatic System				
Thrombocytopenia	4	2	0	1
Neutropenia	0	1	1	1
Anemia	0	1	1	0
Coagulation Disorder	1	0	1	0
Leukopenia	0	0	1	0
Respiratory System				
Laryngismus	2	2	0	0
Skin And Appendages				
Rash	3	2	0	0

CONCLUSION: IDEC-C2B8 given once weekly for four intravenous infusions in doses of 125, 250, or 375 mg/m^2 is safe and well tolerated and has significant clinical activity in patients with relapsed low-grade or follicular lymphomas. The clinical activity and safety profile of this agent compares favorably with other therapeutic alternatives.

SYNOPSIS #2 (Protocol 102-05)

INVESTIGATORS: This study was conducted at 31 sites in the United States and Canada. The project clinician at IDEC Pharmaceuticals was Antonio J. Grillo-López, M.D.

OBJECTIVES: Primary study objectives were:
1) To evaluate the clinical efficacy (overall response rate, time to progression [TTP], and progressive disease-free interval) of 375 mg/m^2 of IDEC-C2B8 given weekly times four,
2) To characterize the safety (qualitative, quantitative, duration, and reversibility) of repeat doses of IDEC-C2B8, and
3) To determine the pharmacokinetics of repeat doses of IDEC-C2B8.

STUDY DESIGN: This was a Phase III, multiple-dose, open-label study in which patients received 375 mg/m^2 of IDEC-C2B8 once weekly times four. Patients were followed for toxicity evaluations and for a clinical response.

PATIENT POPULATION: The study population consisted of patients with histologically confirmed low-grade or follicular non-Hodgkin's lymphoma (NHL), who had relapsed disease (no more than four relapses) or had failed primary therapy. Tumors were reactive with the CD20 antigen. Patients had acceptable hematological status and renal and hepatic function prior to treatment.

STUDY TREATMENT: IDEC-C2B8 was given as a single 375 mg/m^2 intravenous infusion once weekly for four infusions.

Efficacy analyses:
Overall, complete and partial response rates and response durations were calculated for the ITT population, the efficacy, and evaluable subpopulations. The assessment of objective clinical response was performed in 3 ways: assessment by clinical investigators, assessment by the sponsor, and assessment by an independent panel. The primary efficacy analysis as proposed by the sponsor was overall response rate (ORR) based upon response assessment by the independent panel in the evaluable population. As a basis for approval, the sponsor had been informed that the ORR in the ITT population using the designation of response by the independent panel would be utilized by FDA.

An independent panel (LEXCOR) evaluated 3 different sets of CT scans in order to assign a clinical response for all patients with at least a 40% reduction in overall tumor size as assessed by the investigator. The CT scans evaluated were (1) baseline scans, (2) efficacy evaluation scans done on day 50, and (3) the 28th day confirmation response scans (study day 78). The LEXCOR response assessment was used for these patients and the sponsor-assigned response classification (SD or PD) was used for patients not evaluated by LEXCOR.

PATIENT CHARACTERISTICS AND DISPOSITION: The study was conducted in 61 females and 105 males aged 22-79 years (median age 58 years). Patient characteristics included: 91% Caucasian, 78% stage III/IV at initial diagnosis, and 20% type A, 40% type B, 32% type C, 6% type D, and 2% other histologies. All patients had progressive disease requiring treatment and had received at least one therapy (median three, range one to ten) prior to entry. At least one additional reason for treatment was noted in 98 patients (59%) including "B" symptoms (weight loss, fever, and night sweats), bone marrow involvement with lymphoma, abnormal blood count, and pain. Most patients (97%) had received chemotherapy; 25% had received radiotherapy; 4% had undergone bio-immunotherapy, and 14% had been treated with ABMT. Time from initial diagnosis to study entry was a median of 4.1 years (0.5 to 25 years). Of the 166 enrolled patients, 161 completed all infusions. One patient withdrew due to personal reasons prior to treatment. The remaining four were withdrawn due to adverse clinical experience and/or investigator judgment.

STUDY POPULATION- PROTOCOL 102-05 n=166	
Baseline entry variable	**Results**
Gender	
Male	105 (63%)
Female	61 (37%)
Age	
25% quartile	48 years
50% quartile	58 years
75% quartile	66 years
Ethnic background	
Caucasian	151 (91%)
African-American	2 (1%)
Hispanic	5 (3%)
Asian	3 (2%)
Other∝	5 (3%)
IWF classification	
A†	33 (20%)
B	67 (40%)
C	53 (32%)
D	10 (6%)
Other‡	5 (3%)
Patients with tumor-related symptoms	
B symptoms	13 (8%)
Cytopenias	20 (12%)
Pain	19 (11%)
Number of prior chemotherapy regimens	
0*	5 (3%)
1	51 (31%)
2	36 (22%)
3	49 (29%)
4	16 (10%)
5-7	9 (5%)
Prior treatment	
Chemotherapy	161 (97%)
Radiotherapy	42 (25%)
Stem cell transplantation	23 (14%)
Biological therapy**	6 (4%)

†: All SLL (small lymphocytic lymphoma, [IWF 1a]) histology. No IWF 1b patients were enrolled.

‡: Includes one patient with atypical lymphoid infiltration consistent with low-grade B-cell NHL (Site 7, pt. 58); one patient with low-grade monoclonal kappa B-cell process suggestive of marginal zone lymphoma (MALT; Site 8, pt. 166); and one patient with MALT (Site 18, pt. 104).

* Pt. 159, IWF St. B (had bioimmunotherapy x 1, and XRT x 5); Pt. 010, IWF St. A (had XRT x 2); Pt. 103, IWF St. B (had XRT x 1); Pt. 060, IWF St. C (had XRT x 3); Pt. 163, IWF St. B (had XRT x 1).

** Pt. 159, IWF St. B (**immunotoxin w/ricin** →CR for 11 mos.); Pt. 145, IWF St.C (**campath1h**→SD for 23 mos.); Pt. 162, IWF St. C (**immunotoxin w/ricin** →MR for 3 mos.); Pt. 129, IWF St. C (**Sandoz#833** →SD for 4 mos.); Pt 042, IWF St. C (**shared anti-idiotyp.MoAb**→CR for 18 mos.); Pt. 144, IWF St. C (**INF-alpha**→SD for 6 mos.)

∝ The 5 patients in this catagory were (1) Portugese, (2) 2 Pacific Islanders, (3) an East Indian and (4) a Filipino.

@ **Chemorefractory** (or **chemoresistance**) is defined as non-response to chemotherapy in one or more of the following manner: to the 1st course; to any intervening course; to the last course; to all courses; or a duration of <3 months after the last chemotherapy.

EFFICACY: Fifteen patients were excluded from efficacy analysis due to major protocol violations.

SUBSETS OF STUDY POPULATION - PROTOCOL 102-05	
Study Population	Reasons for exclusion
Efficacy population (n=161)	withdrawal for personal reasons prior to treatment (n=1)
	withdrawn due to adverse clinical experience (n= 4)
Evaluable, efficacy population (n=151)	Received concurrent steroids (n=8)
	Surgery (splenectomy) within 4 weeks of study entry (n = 1)
	No measurable disease (n = 1)

The following ten patients who were ineligible for the study were included in all analyses:

- Patient 025 had a history of basal cell carcinoma.
- Patient 060 had a unilateral bone marrow biopsy only.
- Patient 086 had histologic documentation by lymph node biopsy on June 13, 1995 and began treatment December 20, 1995 (>6 month interval).
- Patient 098 had bilateral pleural effusions too small to tap for cytology, with no pleural invasion.
- Patient 105 had a baseline CT scan 33 days prior to treatment.
- Patient 113 was required to have an additional blood draw for serum alkaline phosphatase testing prior to the first infusion.
- Patient 114 had stage I (node negative) lung cancer less than five years prior to study.
- Patient 129 had a pleural effusion too small to tap for cytology.
- Patient 133 had a bone marrow biopsy instead of a lymph node aspiration/biopsy to confirm histology for study entry.
- Patient 152 had baseline hematology and serum chemistry assessments more than one month prior to first infusion of study drug.
- Patient 158, who was inevaluable due to concurrent steroid use also had missing baseline data for tumor measurements (chest CT within one month of study drug infusion).

Evidence of objective clinical responses was consistently observed across all sites enrolling 5 or more patients in the study.

Protocol 102-05
Consistency of response rate across sites¶

Study site	Total number of patients enrolled	Total number of responders (%)
ALL	166	80 (48%)
1	7	3 (43%)
3	5	3 (60%)
5	5	3 (60%)
6	9	6 (67%)
7	8	5 (62%)
8	8	4 (50%)
9	5	1 (20%)
11	12	8 (67%)
14	23	11 (48%)
16	5	2 (40%)
17	6	1 (17%)
18	5	2 (40%)
20	11	4 (36%)
22	6	3 (50%)
32	5	2 (20%)
41	8	5 (62%)

¶ All sites with enrollment of ≥ 5 subjects

LEXCOR (the independent panel of lymphoma experts) evaluated CT scans and assigned a clinical response for all patients with at least a 40% reduction in overall tumor size as assessed by the investigator. The LEXCOR response assessment was used for these patients and the sponsor-assigned response classification (SD or PD) was used for patients not evaluated by LEXCOR. Of 166 patients in the intent-to-treat population, 10 (6%) had a CR and 70 (42%) had a PR, for an overall response rate of 48% (80/166). The assessment of objective clinical responses by the various evaluators (clinicians, sponsor, and independent review panel [LEXCOR]) were highly correlated. Ninety (90) patients were reported by the investigators as having 40% shrinkage of tumor; 1 - 2 patients were noted to have < 40% tumor shrinkage. Of these, 80 (96.3%) were also judged to have attained an objective clinical response by the LEXCOR independent review panel.

PROTOCOL 102-05: Primary and Secondary Efficacy Analyses					
Study Population	Efficacy variables				
	Overall response rate (%), [95% CI]	Complete Response Rate	Partial Response Rate	Median Duration of Response in months (range)	Median Time to Progression for responders in months (range)
ITT (n=166)	80/166 (48%) [40%,56%]	10/166 (6%)	70/166 (42%)	9.2+ (1.9 -18.8+)	11.8+ (3.6 - 20.5+)
Efficacy (n=161)	80/161 (50%) [40%, 56%]	10/161 (6%)	70/161 (43%)	9.2+ (1.9 -18.8+)	11.8+ (3.6 - 20.5+)
Evaluable for efficacy (n=151)	76/151 (50%) [42%, 59%]	9/151 (6%)	67/151 (44%)	9.1+ (1.9 -18.8+)	11.8+ (3.6 - 20.5+)

The median time to onset of response in the 80 responders was 50 days (range 21 to 288); median time to progression has not been reached after 9.0+ months (range 3.2+ to 13.6+) observation; and median response duration has not been reached after 5.9+ months (range 0.9+ to 12.0+) observation. Only 24 of the 80 (30%) responders have relapsed. Nine of 151 evaluable patients (6%) had a CR and 67 (44%) had a PR, for an overall response rate of 50% (76/151). For the 76 evaluable responders, median time to onset of response and to disease progression was the same as for the 80 responding patients, and the median duration of response for this group has not yet been reached, with a median of 6.5+ months observation. No statistically significant differences in response duration in responders were noted after IDEC-C2B8 treatment compared with last course of chemotherapy or last course of therapy. The median absolute B-cell count at baseline in peripheral blood (PB) was 97.5 cells/ml, measured by both CD19 and CD20 cell markers. Evaluation of peripheral blood for CD19+ cells following IDEC-C2B8 treatment showed effective depletion of circulating B cells.

Overall tumor size was reduced by 20% in 76% of patients; responders had a > 50% reduction in the mean sum of the products of the perpendicular diameters (SPD) of measured lesions following treatment. Mean SPD continued to decrease until stabilizing four months after therapy. Average lesion reduction in patients with a CR, PR, and SD was 85%, 76%, and 39%, respectively. "B" symptoms and other disease-related signs and symptoms were reported in 22 of the 80 responders. Symptoms resolved in all patients; recurred transiently in two patients and recurred and persisted in one. A univariate statistical analysis (Fisher's Exact Test) was performed to compare response to IDEC-C2B8 therapy versus patient characteristics at initial diagnosis and at baseline, and versus prior treatment.

A significantly higher response rate was associated with the following parameters: histologic types B, C, and D versus type A, prior ABMT therapy, positive bcl-2 status, and no bone marrow involvement at baseline. A significant relationship was noted between the number of relapses and response: a higher number of relapses was associated with a lower response rate. A nonsignificant trend of increasing response rates with fewer prior chemotherapy courses was observed. Resistance to first, last, any intervening, or all chemotherapy courses had no significant effect on response to treatment. No statistically significant relationship was noted between response and age, stage of disease, years since diagnosis, performance status, serum LDH level, β_2-microglobulin levels, and extranodal involvement at initial diagnosis and/or at baseline.

Effect of C2B8 on tumor-related symptoms

Tumor-related symptoms were reported in 39 patients, 23 of whom had objective clinical responses. These symptoms included night sweats, fever, weight loss, pain, urticaria, and nodal itching. Relief of tumor-

associated symptoms was more consistently observed in patients with objective clinical responses (see the following tables). All tumor-related symptoms resolved by the fourth week of treatment in 17 of 23 patients with objective clinical responses. Symptoms resolved by 3 months post-treatment (n=1) and 6 months post-treatment (n=2) in an additional 3 patients in whom objective responses were observed. With regard to the remaining 3 patients, there was inadequate information on one to determine what tumor-related symptoms were present and whether resolution occurred. In the second patient (#157), fever and weight loss resolved by the fourth week of treatment; however night sweats persisted and additional symptoms (not specified) emerged at 3 months post-therapy. The third patient (#129) had persistent chest and abdominal pain, with the development of B symptoms at five months post-therapy.

The effect of C2B8 on tumor-related symptoms in 16 patients without evidence of objective tumor responses is provided in detail in tabular form. Eight of the 16 patients experienced resolution of symptoms by the fourth week of therapy with two additional patients experiencing resolution of symptoms by the third (#059) and sixth (#058) months post-treatment. Symptoms persisted in three subjects (#045, #158, and #149) and one subject was reported to have "intermittent improvement" (#161). In one subject, the "B" symptom(s) was not specified and there is insufficient information to determine whether any resolution occurred (#044). In the final patient, the onset of tumor-related weight loss was not documented until 6 months after therapy.

EFFECT OF C2B8 ON TUMOR-RELATED SYMPTOMS IN PTS. WITH OBJECTIVE CLINICAL RESPONSES					
Pt. #	**"B" symptom***	**Resolution (study date)**	**Tumor-related pain**	**Resolution (study date)**	**Response**
036	Night sweats	week 4	Upper chest	week 4	PR
111	NONE	N/A	Abdominal	week 4	PR
098	NONE	N/A	R.rib cage	month 6	PR
050	NONE	N/A	L. abdomen	month 3	PR
038	Night sweats	month 6	Abdominal	week 4	PR
006	Wt. Loss	week 4	NONE	N/A	PR
031	Wt. Loss	Onset at month 12	Chest/abdomen	week 4	PR
035	NONE	N/A	R. leg pain	week 4	PR
020	Unknown	Unknown	NONE	N/A	CR
004	NONE	N/A	NHL-assoc. urticaria	week 4	CR
041	NONE	N/A	Splenomegalic pain	week 4	CR
129	Wt. Loss Recur. fever Night sweats	Onset at month 5	Chest and abdomen	none	PR
157	Wt. Loss Recur. Fever Night sweats	week 4 (fever, wt loss) none- night sweats.	Unspecified	Onset at month 3	PR
042	NONE	N/A	Chest pain	week 4	PR
104	NONE	N/A	Esophageal cramp.	week 4	PR
053	Fever; Night sweats	week 4 for both	L. Neck pain	week 4	CR
163	Recur. Fever	week 4	Unspecified	4 wks post-tx	CR
021	NONE	N/A	L. Jaw pulling	week 4	PR
146	Night sweats	week 4	NONE	N/A	PR
049	Night sweats	week 4	Unspecified	Unspecified	CR
154	Night sweats	week 4	NONE	N/A	PR
148	NONE	N/A	Back pain	week 4	PR
133	Night sweats	week 4	NONE	N/A	PR

"B" symptoms defined as (1) unexplained weight loss or > 10% during the past 6 months; (2) unexplained persistent or recurrent fever (> 38°C) during the past month; and (3) recurrent drenching night sweats during the past month.

EFFECT OF C2B8 ON TUMOR-RELATED SYMPTOMS IN PTS. WITHOUT OBJECTIVE CLINICAL RESPONSES				
Pt. #	**"B" symptom***	**Resolution by study date**	**Tumor-related pain**	**Resolution by study date**
003	None	N/A	LUQ abdomen	week 4
017	Wt. Loss	Onset at month 6	NONE	N/A
065	NONE	N/A	Generalized	week 4
058	NONE	N/A	Thoracic	month 6
083	NONE	N/A	Back pain	week 4
045	Recur. Fever Night sweats	none	NONE	N/A
138	Night sweats	week 4	NONE	N/A
079	Night sweats	week 4	NONE	N/A
044	Unknown	Unknown	NONE	N/A
059	NONE	N/A	Abdominal	month 3
158	Recur. Fever Night sweats	none	Itching (nodal)	none
081	Recur. Fever Night sweats	week 4	NONE	N/A
161	NONE	N/A	Abdominal	Intermittent
149	Night sweats	none	NONE	N/A
153	Night sweats	week 4	NONE	N/A
109	Weight loss	week 4	NONE	N/A

* "B" symptoms defined as (1) unexplained weight loss or > 10% during the past 6 months; (2) unexplained persistent or recurrent fever (> 38°C) during the past month; and (3) recurrent drenching night sweats during the past month.

Comparison of Response Duration with that of last Chemotherapy Regimen

A planned secondary analysis was conducted comparing the duration of response to C2B8 with the duration of response to the most recent chemotherapy regimen. The overall response rate to C2B8 was lower than the response rate to most recent chemotherapy regimen [50% ORR to C2B8 vs. 73% (117/161) to last chemotherapy]. A comparison of the overall and complete response rates and the duration of response to C2B8 vs. the response rates and duration of response to most recent chemotherapy regimen was conducted in the subset of 80 patients who had responded to C2B8. The overall and complete response rates and the response duration to the most recent chemotherapy regimen were higher. The majority of patients who responded to C2B8 had responded to the most recent chemotherapy regimen (81%), and approximately half (41/78) had had a complete response to the most recent chemotherapy regimen.

COMPARISON OF C2B8 RESPONSE RATE AND DURATION TO MOST RECENT CHEMOTHERAPY

Population	Overall response rate	Complete response rate	Response duration
C2B8 responders: Response to C2B8 (n=78)	78/161 (48%)	lo/161 (6%)	9.2 + months
C2B8 responders: Response to prior chemotherapy (n=78)	63/78 (81%)	41/78 (53%)	20.0 months
All patients with response to last chemotherapy (n=l17)	117/161 (73%)	60/161 (37%)	12.0 months

The next table provides the results of overall and complete response rates and response duration to C2B8, according to the number of prior chemotherapeutic regimens. Of note, neither the overall nor complete response rate decreased with an increasing number of prior chemotherapeutic regimens. The response duration data are not mature enough to make an assessment on whether the duration of response to C2B8 varies according to extent of prior therapy.

DURATION OF RESPONSE, BASED ON THE NUMBER OF PREVIOUS CHEMOTHERAPEUTIC COURSES

Prior Chemotx Courses	ORR	CR	Median Duration of Response (months)
0	40% (2/5)	0%	8.6+
1	59% (30/51)	8% (4/51)	9.1+
2	31% (11/36)	6% (2/36)	9.8+
3	49% (24/49)	4% (2/49)	8.1+
≥4	52% (13/25)	8% (2/25)	9.2+
All	48% (80/166)	6% (10/166)	9.2+

Exploratory analyses

Baseline variables correlated with clinical response

I. An exploratory analysis was conducted to evaluate pretreatment variables which were associated with the attainment of an objective clinical response. In a stepwise logistic regression analysis, the following variables were significantly associated with clinical response:

VARIABLES CORRELATING WITH CLINICAL RESPONSE

Variable	χ^2	p-value
Histologic subtype (B,C, D vs. A)	22.9	<0.001
Prior ABMT (yes vs. no)	4.97	0.03
bcl-2 status at entry (positive vs. negative)	4.76	0.03
age (< 60; ≥ 60)	3.63	0.06
Bulky disease (< 5 cm; 5-7 cm; 7-10 cm)	3.74	0.05
refractory disease (yes vs. no)	3.08	0.08
# of prior chemotherapy courses	0.24	0.6

The following variables were correlated with attainment of an objective clinical response: International Working Formulation classification B, C, and D histology as compared to subtype A; a history of prior autologous bone marrow transplantation; evidence of bcl-2 in marrow or lymph nodes; lesion size less than 5 cm.; age < 60 years; and lack of bone marrow involvement at study entry. Variables which were not statistically correlated with attainment of objective clinical response in the multivariate analysis were: gender; low grade vs intermediate grade histologic subtype (A-C vs. D); years since diagnosis; extranodal disease; elevated LDH values; serum antibody levels; and β2-microglobulin level. An additional analysis was performed with pooled data from patients on studies 102-05 and 102-02 .

A significant relationship was noted between the number of relapses and response: a higher number of relapses was associated with a lower response rate. Resistance to first, last, any intervening, or all chemotherapy courses had no significant effect on response to treatment.

II. *Comparison To Single-Agent Efficacy In Comparable Studies Reported In The Medical Literature*: A brief summary of studies in literature are compared with the results of the IDEC C2B8, as noted in Table 9 below. The single-agent therapies selected were fludarabine and cladribine, because they are the most frequently used single-agent therapies in relapsed patients. Six studies were identified from the published literature that fulfilled specified criteria (defined by the sponsor) for use as historical controls.[1] Most studies reported results from evaluable patients and not intent-to-treat populations; only one indicated specifically that patients were

[1] The following criteria were used for study selection: (1) study published as a full paper, not an abstract; (2) study conducted in the same timeframe as 102-05, after CT scanning became broadly available; (3) study included patients with low-grade or follicular cell NHL who had relapsed following, or were refractory to, previous chemotherapy and (4) study included at least 20 patients. Characteristics of the patients could be ascertained from the study: (1) patients were treated with a single agent and (2) demographic information including age, sex, stage of disease, histology, and use of previous chemotherapy was available.

entered consecutively. When all studies are considered, the overall response rate for fludarabine (48%) and for cladribine (52%) is not appreciably different from that of C2B8 (48%).

PROTOCOL 102-05 -- Supportive Data				
Population	Time to progression (median in months)	Response rate	CR rate	Response duration in months (range)
102-05 (n=166)	7.6 (0-20.5+)	48%	6%	9.2+ mos (1.9-18.8+)
Fludarabine				
Whelan (1991); n=34	N/A	39%	18%	N/A
Hiddemann (1993); n=45	N/A	31%	13%	N/A
Pigaditou (1993): 45 evaluable pts	N/A	45%	9%	N/A
Falkson (1996): 21 evaluable pts	4.6	62%	33%	N/A
Cladribine				
Kay (1992) 40 pts	N/A	43%	20%	6 mos
Hoffman (1994) 21 pts	N/A	43%	14%	N/A

1. Whelan JS, Davis CL, Rule S, Ranson M, Smith OP, Mehta AB, et al. Fludarabine phosphate for the treatment of low-grade lymphoid malignancy. *British Journal of Cancer* 1991;64:120-123.
Whelan et al. treated 34 patients with advanced, low-grade NHL who had failed previous chemotherapy with fludarabine 25 mg/m^2 for five days every 21 to 28 days. The mean number of cycles was three (range 1 to 10). The CR rate was 18% and the PR rate was 21%.

2. Hiddemann W, Unterhalt M, Pott C, Wormann B, Sandford D, Freund M, et al. Fludarabine single-agent therapy for relapsed low-grade non-Hodgkin's lymphomas: a phase II study of the German Low-Grade Non-Hodgkin's Lymphoma Study Group. *Seminar in Oncology* 1993;20(5 Supplement 7):28-31.
Hiddemann et al. treated 45 patients with advanced low-grade NHL who had failed first-line chemotherapy with fludarabine, 25 mg/kg/day over five consecutive days, repeated every four to five weeks. All patients completed at least two courses of therapy. The CR rate was 13% and the PR rate was 18%.

3. Pigaditou A, Rohatiner A, Whelan J, Johnson P, Ganjoo R, Rossi A, et al. Fludarabine in low-grade lymphoma. *Seminars in Oncology* 1993;20(5 (Suppl. 7)):24-27.
Pigaditou et al. accrued 88 patients between 1989 and 1993 with low-grade NHL. Fifty-one of these patients were stated to have recurrent/resistant disease. Treatment consisted of fludarabine, 25 mg/m^2, administered daily for five days and repeated at 21 to 28 day intervals. Information on the number of courses of treatment was not provided. Among the 45 patients who were considered evaluable, 9% had a CR and 36% had a PR.

4. Falkson (1996) Fludarabine: A phase II trial in patients with previously treated low-grade lymphoma. *American Journal of Clinical Oncology* 1996;19(3):268-270.
Falkson evaluated the use of fludarabine in 22 patients with low-grade NHL identified as no longer responding to standard treatment. Fludarabine, 25 mg/m^2, was administered daily for five days and

repeated at 28-day intervals. Information on the number of treatment courses was not provided. Among 21 evaluable patients, 33% had a CR and 29% had a PR. The median time to treatment failure was 4.6 months.

5. Kay AC, Saven CJ, Carerra DA, Carson D, Thurston D, Beutler E, et al. 2-Chlorodeoxyadenosine treatment of low-grade lymphomas. *Journal of Clinical Oncology* 1992;10(3):371-377.
Kay et al. accrued 40 patients with low-grade NHL that was recurrent or refractory to previous treatment from 1987 to 1990. In six patients, the disease had histologically transformed to a higher grade. Patients were treated with cladribine, 0.1 mg/kg/daily for seven consecutive days and repeated every five weeks. Patients received one to six (median of three) courses of therapy. The CR rate was 20% and the PR rate was 23%. The duration of CR was 1 to 33 months (median of six months) and the duration of PR was 3 to 6 months.

6. Hoffman M, Tallman MS, Hakimian D, Janson D, Hogan D, Variakogis D, et al. 2-Chlorodeoxyadenosine is an active salvage therapy in advanced indolent non-Hodgkin's lymphoma. *Journal of Clinical Oncology* 1994;12(4):788-792.
Hoffman et al. accrued 21 patients with recurrent/resistant NHL between 1990 to 1993. Cladribine was administered at 0.1 mg/kg/day for 5 to 7 consecutive days and repeated every 28 days. Patients received one to seven (median two) courses of therapy. The CR and PR rates were 14% and 29%, respectiively.

Safety

All adverse events, regardless of relationship to treatment or severity, were collected for 30 days post-treatment, and serious adverse events or related events were collected for up to one year from treatment onset. Adverse events were categorized according to temporal relationship to study drug treatment in the following manner: 1) adverse events observed during the treatment period and up to 30 days after the last dose (refer to the next table); 2) adverse events observed from 31 days after the last dose of drug until one year; 3) adverse events which existed prestudy and continued during the study period and those for which the beginning and/or ending date were unavailable.

One hundred fifty-eight of 166 patients (95%) experienced adverse events. A total of 1163 adverse events were reported. During the treatment period, 843 adverse events (72%) were reported in 149 patients. Of these, 549 events of grade 1 severity were reported in 57 patients, 254 events of grade 2 severity were reported in 74 patients, 34 events of grade 3 severity were reported in 15 patients and 3 events of grade 4 severity were reported in 3 patients (severity grade for 3 events are not available).

Of 733 adverse events which were identified by investigators as possibly or probably related to the study drug, 621 (85%) were reported in 140 patients during the treatment period, 98 (13%) were reported in 45 patients during long-term follow-up, and 14 events (2%) with onset prestudy or chronology unknown occurred in 7 patients.

OVERVIEW OF ADVERSE EVENT RATES				
	Adverse Events	# of subjects reporting events	"related" adverse events	# subjects reporting "related" AE's
Total	1163	158	733	
During treatment	843/1163 (72%)	149	621/733 (85%)	40
During follow-up	206/1163 (18%)	75	98/733 (13%)	45
Prestudy/unknown	110/1163 (9%)	63	14/733 (2%)	7

The most frequent adverse events were fever (46% of patients), chills (30%), and nausea (24%). The incidence of adverse events was highest during the first infusion of study drug. Adverse events of particular concern and also were associated with study drug infusion included hypotension, bronchospasm, arrhythmias, and angioedema.

Nineteen episodes of hypotension were reported in 16 patients (10%) during the treatment period. In 3 of these patients, C2B8 was discontinued due to this event. Of the 19 episodes reported, 11 were Grade 1, seven were grade 2, and one was grade 3 in severity. Five patients required "medication" (consisting of IV saline and/or acetaminophen and diphenhydramine); no patient received vasopressors. In the remainder of the patients, hypotension resolved with temporary interruption and/or slowing of infusion; some subjects also received intravenous saline administration.

Nineteen episodes of bronchospasm were reported in 17 patients, including 14 grade 1, 4 grade 2 and 1 grade 3 event. In addition to bronchospasm, other pulmonary symptoms, were observed, such as rhinitis (11% of patients) and cough increase (7% of patients).

Nine episodes of arrhythmia was reported in five patients; four grade 1, two grade 2, one grade 3, and one grade 4 event were reported. One subject, in whom arrhythmias were noted during the first two infusions experienced a grade 4 arrhythmia observed during the third infusion. In addition, bradycardia, which was reported separately, was observed in 6 patients, in whom 7 grade 1 and one grade 2 event were reported.

Impact on the Immune System:
Administration of C2B8 results in a rapid and prolonged depletion of circulating B lymphocytes (CD19+ and CD20+ cells) . Serial evaluation of the peripheral blood mononuclear cells by flow cytometry demonstrated that recovery to normal levels was not observed until 12 months after completion of therapy. Mean serum IgG and IgA levels remained within the normal range. Mean serum IgM levels were slightly elevated one-month post-treatment and slightly reduced at eight-months post-treatment.

Sixty-eight infectious events were reported in 50 patients. Of the six grade 3 infectious events specifically identified by the sponsor, none occurred in association with neutropenia. All infectious events which occurred during the treatment period were reported; late infections (study day 31 to 365) provided for patients only for those who required hospitalization. During the treatment period, three patients were diagnosed with infections (sinusitis on study day 3, Listeria infection on study day 15, and gastroenteritis on study day 27). A more detailed description of the subject with Listeria infection is provided below. Late infectious events included pneumonia in 5 patients and one patient each who was hospitalized with the following: an upper respiratory tract infection, sinusitis, myofascial infection, and Herpes simplex. Reactivation of ophthalmic Herpes zoster also occurred both during and after the study period in one patient. Three patients had documented

infections with positive blood cultures, one of these occurred during the study period and two were late infectious events. Details regarding these three patients are as follows:

- Prior to his third infusion, on study day 15, Patient #018 presented with flu-like symptoms. Blood cultures were positive for Listeria. The patient responded to antibiotic therapy.
- Patient 099 had a prestudy splenectomy. This subject was hospitalized for pneumonia (Pseudomonas species) on study day 91 and recovered. Blood cultures obtained on study day 135 were positive for Staphylococcal bacteremia.
- Patient #155 was reported to have grade 2 fever and chills and grade 3 infection requiring hospitalization. Polymicrobial bacteremia was reported on day 42, which was believed to be catheter-related. The infection resolved with IV antibiotics.

Serious and Severe/Life-threatening (Grade 3 /4) Adverse Events

Thirty-eight patients (23%) experienced 72 (6%) Grade 3 or 4 adverse events; 9 additional patients (5%) experienced 50 (4%) Grade 3 or 4 laboratory abnormalities. The following 33 grade 3 toxicities which were not directly attributable solely to the underlying malignancy were reported among 15 patients: chills, vomiting, anemia (reported in 3 patients each), headache, back pain , and leukopenia, (reported in 2 patients for each), hypotension , angioedema, urticaria, bronchospasm, dyspnea, increased cough, rhinitis, arrythmia, diarrhea, thrombocytopenia , pain [site not specified], skin pain, pruritis, sinusitis, infection [not otherwise specified] and asthenia (1 patient each). There were 2 patients with grade 4 toxicities, possibly related to treatment. These were arrhythmia and neutropenia. Adverse events of particular concern, and which led to discontinuation of treatment, included grade 3 hypotension, bronchospasm, angioedema with dyspnea,, and grade 4 arrhythmia. There were a number of patients who required hospitalization for adverse events. During the treatment period this was predominantly for infection (sinusitis on study day 3 and Listeria infection on study day 15) and infusional toxicities (fever and rigors on day 1 and fever on day 8 in two different patients) . Late toxicities which required hospitalization included 5 patients hospitalized with pneumonia, two with gastroenteritis, one each with an upper respiratory tract infection, sinusitis, myofascial infection, and Herpes simplex. There were also two patients hospitalized with late cardiac events (CHF on study day 164 and CHF in association with myocardial infarction on study day 144. The other late toxicity of note is a single subject who developed aplastic anemia on study day 79; this event was rated by the investigator as possibly related to study drug. (Refer to the tables in the Appendices).

One adverse event attributable to C2B8 resulted in permanent disability. This was a finding visual abnormality in a patient with a prior history of ophthalmic Herpes zoster . The patient's symptoms recurred following treatment with C2B8, and a diagnosis of retinal necrosis of the right eye due to the Herpes zoster was made.

A squamous cell skin carcinoma was excised from patient 153 approximately three weeks prior to study entry. The carcinoma recurred approximately three weeks following entry and was considered to be unrelated to C2B8 treatment.

Adverse events leading to discontinution of study drug

Four patients (2%) discontinued the C2B8 therapy due to Grade 3 or 4 adverse events. These three patients were all discontinued on study day one following the onset of these infusion-related symptoms:

- Patient 028 experienced Grade 3 events of angioedema, dyspnea, and rhinitis during the first infusion. This patient reported respiratory illness prior to the onset of the study. The patient received diphenhydramine, acetaminophen, and hydrocortisone and recovered.
- Patient 118 was discontinued due to Grade 3 hypotension accompanied by Grade 1 bronchospasm, chills, dizziness, fever, and nausea during the first infusion. Bronchospasm and chills lasted less than 15 minutes, fever duration was 1 hour, and nausea was reported for 5.5 hours. The patient responded to IV saline; no vasopressors were required.
- Grade 3 adverse Clinical Study Report: Protocol 102-05 events of bronchospasm, chills, cough, nausea, and vomiting during the first infusion were reported for patient 061. The patient was hospitalized and

symptoms were controlled within one hour.

Patient 092 experienced Grade 2 arrhythmia during the first two infusions of IDEC-C2B8and hospitalized for the third infusion. During this infusion, Grade 4 arrhythmia was observed and the infusion was stopped. The patient recovered and was discontinued from the study.

Mortality within one year of study drug

Four patient deaths occurred at 2.6 to 11.6 months after the first infusion. Each of these deaths was attributed to the non-Hodgkin's lymphoma. Three of the subjects (007, 062, and 094) had received additional anti-neoplastic therapy after C2B8.

Immunogenicity

One of 166 patients (0.6%) developed a human anti-chimeric antibody (HACA) response. This was detectable but below the limit of quantification at day 50; a HACA response was not detectable on serum samples obtained on days 43 and 99.

PHARMACOKINETICS: IDEC-C2B8 serum concentrations were higher for responders compared with nonresponders at all time-points both during (pre- and post-infusion) and after treatment. This difference reached levels of statistical significance prior to the second infusion, prior to the fourth infusion, after the fourth infusion, and at 1 week, 4 weeks, and 13 weeks post-treatment. A negative correlation occurred between IDEC-C2B8 serum concentration versus the number of circulating B cells at baseline, the baseline value of the maximum diameter of the largest lesion, and the baseline SPD of the six largest lesions. IDEC-C2B8 serum concentration during and after treatment was significantly lower in histologic type A lymphoma patients compared with type B, C, and D patients. The value of Cmax increased between the first and fourth infusions. The mean serum half-life of IDEC-C2B8 was 76 hours after the first infusion and 206 hours after the fourth infusion, with a significant positive correlation between the number of circulating B cells at baseline and clearance after the first infusion. No statistically significant difference was found between pharmacokinetic parameters and response to IDEC-C2B8 therapy. In addition, patient age had no effect on the pharmacokinetics or the clinical response to IDEC-C2B8.

CONCLUSION: IDEC-C2B8 given once weekly for four 375 mg/m^2 intravenous infusions is safe and well tolerated and has significant clinical activity in patients with relapsed low-grade or follicular B-cell NHL (IWF: A, B, C, and D).

Integrated Efficacy and Safety Studies

The sponsor has conducted 7 clinical studies, three of which are ongoing and four have been completed. The data submitted in support of efficacy are derived from 203 subjects enrolled in two protocols, IDEC 102-05 (n=166) and IDEC 102-02 (37 of the 47 subjects enrolled, treated at the same dose and schedule as in IDEC 102-05). Safety data are submitted for all patients (n=282) enrolled in single agent studies of IDEC C2B8 [does not include data for patients from Protocols 102-03 and 102-07].

INTEGRATED EFFICACY SUMMARY

The results of Protocols 102-02 and 102-05 are confirmatory in demonstrating similar response rates and durability in multicenter settings using the same dose and schedule of C2B8. The results for the primary and secondary efficacy results are from both studies are provided in tabular form.

IDEC Integrated Summary Regarding **Efficacy** [Trials for C2B8 (RITUXAN)]

	Pivotal trial: Protocol 102-05	Supportive trial: Protocol 102-02
TITLE	**PIVOTAL PHASE III MULTI-CENTER STUDY TO EVALUATE THE SAFETY AND EFFICACY OF ONCE WEEKLY TIMES FOUR DOSING OF IDEC-C2B8 (IDEC-102) IN PATIENTS WITH RELAPSED LOW-GRADE OR FOLLICULAR B-CELL LYMPHOMA**	**PHASE I/II CLINICAL TRIAL TO EVALUATE THE SAFETY AND EFFICACY OF IDEC-C2B8 GIVEN WEEKLY TO PATIENTS WITH B-CELL LYMPHOMA**
STUDY DESIGN	Single arm, multiple-dose, multi-center study. This study was conducted at 31 sites in the United States and Canada.	An open-label, single-arm, multi-center Phase I (dose escalation) and Phase II (clinical activity) study was conducted at seven sites in the U.S.
OBJECTIVES	1. To evaluate the clinical efficacy (overall response rate, time to progression [TTP], and progressive disease-free interval) of 375 mg/m^2 of IDEC-C2B8 given weekly times four, 2. To characterize the safety (qualitative, quantitative, duration, and reversibility) of repeat doses of IDEC-C2B8, and 3. To determine the pharmacokinetics of repeat doses of IDEC-C2B8.	1. Identify a biologically active tolerated dose (BATD) and dose-limiting toxicities (DLTs) for efficacy trials of IDEC-C2B8 given weekly as single intravenous infusions times four in patients with relapsed B-cell lymphoma, 2. Characterize the safety and toxicity profile of IDEC-C2B8, including qualitative and quantitative toxicities, and define their duration and reversibility, 3. Monitor for tumor penetration, IDEC-C2B8 serum levels, human anti-mouse antibody (HAMA), and human anti-chimeric antibody (HACA) levels, 4. Evaluate the pharmacokinetics of intravenous IDEC-C2B8 and 5. Evaluate clinical activity and determine Phase II response rate.
ELIGIBILITY CRITERIA	Patients with histologically confirmed low-grade or follicular non-Hodgkin's lymphoma (NHL, IWF A, B, C, or D), who had relapsed disease (no more than four relapses) or had failed primary therapy. This also includes: • Patients who have failed to respond to ABMT or, if ABMT-responders, have relapsed at least 6 months prior to enrollment. • No more than 4 relapses after STANDARD therapies [chemotherapy , XRT (but not radio-immunotx), and immunotherapy (within 3 weeks of the 1st C2B8 tx; if nitrosurea or mitomycin-C, within 6 weeks), and/or ABMT] or non-responders to the 1st therapies. • Patients must not have bulky disease (any single mass > 10 cm in its greatest diameter, nor small lymphocytic lymphoma with a total lymphocyte count greater than 5000/mm^3	Patients with histologically confirmed B-cell lymphoma; low-grade lymphoma were to have relapsed after at least one, and no more than four, prior standard therapies. Patients with intermediate-and high-grade lymphoma were to have relapsed after at least one, and no more than three, prior standard therapies. This also includes: • Patients who have failed to respond to ABMT or, if ABMT-responders, have relapsed at least 6 months prior to enrollment. • No more than 4 relapses after STANDARD therapies [chemotx , XRT (but not radio-immunotx), and immunotx (within 3 weeks of the 1st C2B8 tx; if nitrosurea or mitomycin-C, within 6 weeks), and/or ABMT] or non-responders to the 1st therapies. • Patients must not have bulky disease (any single mass > 10 cm in its greatest diameter, nor small lymphocytic lymphoma with a total lymphocyte countgreater than 5000/mm^3
TREATMENT PLAN	375 mg/m^2, 150 mg/hour intravenously, weekly x 4.	A single intravenous infusion at a maximum rate of 150 mg/ hour, once weekly x 4. The first dose level: 125 mg/m^2 (3 patients); the second 250 mg/m^2 (seven patients); and the third 375 mg/m^2 (37 patients).
STUDY MONITORING	The 1st post-treatment follow-up will be one month after the 4th dose of IDEC-C2B8; thereafter, follow-up will be at 3-month intervals, with clinical responders followed up to 4 years. [That is to say that, after the first 2 years of follow-up (Years 3 and 4 following treatment) in responders who have not relapsed, patients will be followed at 6-month intervals until either (1) disease-progression, or (2) a maximum of 4 years after completing the treatment.] Patients with progression of disease will be taken off the study. The overall duration of the study will be @ 5 years from patient enrollment to the patient's last follow-up.	The 1st post-treatment follow-up will be one month after the 4th dose of IDEC-C2B8; thereafter, follow-up will be at 3-month intervals, with clinical responders followed up to.4 years. [That is to say that, after the first 2 years of follow-up (Years 3 and 4 following treatment) in responders who have not relapsed, patients will be followed at 6-month intervals until either (1) disease-progression, or (2) a maximum of 4 years after completing the treatment.] Patients with progression of disease will be taken off the study. The overall duration of the study will be @ 5 years from patient enrollment to the patient's last follow-up.

PROTOCOLS 102-05 AND 102-02: COMBINED PRIMARY AND SECONDARY EFFICACY RESULTS			
Study	Overall response rate (% [95% CI])	CR rate	Median Response Duration in months (range)
102-05	80/166 (48%[40%, 56%])	10/166 (6%)	9.2+ (1.9 - 18.8+)
102-02	17/37 (46% [30%, 63%])	3/37 (8%)	8.6 (2.6 - 26.2+)

A multivariate analysis, combining the data from Protocols 102-02 and 102-05, was conducted to evaluate the correlation of patient characteristics at the time of study entry with response status. The factors which correlated strongly with response to therapy included a follicular histology (IWF types B, C, and D), a history of prior autologous bone marrow transplantation, and the absence of bone marrow involvement with lymphoma. Although the number of previous therapies of any kind (chemotherapy, bone marrow transplantation, radiotherapy, or immunotherapy) was identified as a factor which differed significantly between responding and non-responding patients, there appeared to be no clear pattern of diminishing response with increasing number of prior treatments. Similarly, although there was a trend toward a difference in distribution between responding and non-responding patients with regard to number of prior chemotherapeutic regimens, no consistent effect was identified with regard to decreasing response rate with an increasing number of prior chemotherapy regimens. The next table provides the results of the percentage of responding patients with various baseline entry variables which were identified as correlated in the multivariate analysis.

COMPARISON OF BASELINE CHARACTERISTICS FOR RESPONDERS VS. NONRESPONDERS
Combined Data from 102-05 and 102-02

Baseline Entry Variables	Category	Responder (n=97)	Non-responder (n=105)	p value¶
LDH	Normal or Low High	61 (52%) 36 (44%)	57 (48%) 46 (56%)	0.3
Age	< 60 years ≥ 60 years	53 (46%) 45 (51%)	61 (54%) 44 (49%)	0.6
Gender	Female Male	40 (52%) 58 (46%)	37 (48%) 68 (54%)	0.5
Histological Grade	Low Intermediate	91 (48%) 7 (54%)	99 (52%) 6 (46%)	0.8
Histological Type	Type A Type B, C, D	4 (11%) 93 (57%)	33 (89%) 69 (43%)	< 0.0001
Years from Dx	< 5 years 5 - 10 years >10 years	58 (48%) 27 (42%) 13 (68%)	62 (52%) 37 (58%) 6 (32%)	0.14
Bulky Disease	< 5 cm 5 - 7 cm > 7 cm	67 (55%) 20 (38%) 11 (38%)	54 (45%) 32 (62%) 18 (62%)	0.06
Prior ABMT	Yes No	20 (80%) 78 (44%)	5 (20%) 100 (56%)	<0.0001
No. of Previous Therapies	1 2 3 ≥ 4	30 (60%) 18 (37%) 15 (33%) 35 (60%)	20 (40%) 31 (63%) 31 (67%) 23 (40%)	< 0.0001
No. of Previous Chemotx. Courses	0 1 2 3 ≥ 4	2 (40%) 40 (61%) 16 (34%) 26 (46%) 14 (50%)	3 (60%) 26 (39%) 31 (66%) 31 (54%) 14 (50%)	0.08
Bone Marrow Involvement	Yes No	40 (39%) 58 (58%)	63 (61%) 42 (42%)	< 0.0001
Extranodal Disease	Yes No	70 (45%) 28 (60%)	86 (55%) 19 (40%)	0.1

¶ Fisher's Exact Test (2-sided)

INTEGRATED SAFETY SUMMARY

Patient Characteristics

A summary of the studies, including study design, dose and schedule, and number of patients evaluated for safety, is provided in Table 17. A total of 282 subjects have received one or more doses of C2B8 as a single agent. Across all studies, the median age was 56 years (range 22-81). Sixty-one percent of patients were male and 93% were Caucasian. The distribution of histologic subtype of lymphoma (as defined by IWF) was 18% IWF-A, 43% IWF-B, 30% IWF-C, 6% IWF-D, 1% IWF- types E-H, and 2% classified as other. Sixty-one percent had a baseline WHO performance of 0, 28% of patients had a WHO PS of 1, and 2% had a WHO PS of 2. WHO performance status was not available for nine percent of patients.

An integrated summary of the per-patient incidence of all adverse events and of all Grade 3/4 adverse events during the treatment period (the interval from first IDEC-C2B8 infusion until 30 days after last IDEC-C2B8 infusion) is shown in next table.

With regard to Grade 3/4 adverse events observed during the follow-up period, the following are notable in light of the arrhythmias and bradycardia observed during therapy in 6 and 5 patients, respectively, and the one patient in Protocol 102-02 who suffered a myocardial infarction on study.

- Patient 044 (site 14) had a history of chronic obstructive pulmonary disease and hypothyroidism who, on study day 164, had congestive heart failure (CHF), which was ultimately controlled with hospitalization. The relationship between IDEC C2 B8 and CHF was rated as unknown.
- Patient 050 (site 06) with a history of CHF secondary to previous chemotherapy (drug-induced cardiomyopathy) experienced CHF and possible myocardial infarction 4 months after the last treatment with C2B8. This was resolved in one week and felt not to be related to C2B8.

Integrated Summary: All Adverse Events (AE's) w/ All Grade 3/4 AE's During *Treatment*						
	Grade 3		Grade 4		ALL Grades	
	N	(%)	N	(%)	N=282	(%)
A. E. BY ORGAN SYSTEM	36	12.8	7	2.5	**263**	**(93.3)**
GENERAL						
Chills	6	2.1	0	0.0	**98**	**(34.8)**
Headache	3	1.1	0	0.0	**50**	**(17.7)**
Fever -- no Gr. 3 or 4 AE's					**152**	**(53.9)**
RESPIRATORY						
Bronchospasm	4	1.4	0	0.0	**29**	**(10.3)**
Increase in cough	1	0.4	0	0.0	**24**	**(8.5)**
Dyspnea	2	0.7	0	0.0	**12**	**(4.3)**
CARDIOVASCULAR						
Arrythmia	1	0.4	1	0.4	**5**	**(1.8)**
CPK increase (MI)	0	0.0	1	0.4	**1**	**(0.4)**
Hypotension	1	0.4	1	0.4	**29**	**(10.3)**
Angioedema	1	0.4	0	0.0	**36**	**(12.8)**
Hypertension	1	0.4	0	0.0	**13**	**(4.6)**
HEME/LYMPHATIC SYSTEM						
Leukopenia	6	2.1	0	0.0	**25**	**(8.9)**
Neutropenia	2	0.7	3	1.1	**20**	**(7.1)**
Thrombocytopenia	3	1.1	2	0.7	**26**	**(9.2)**
Anemia	4	1.4	0	0.0	**13**	**(4.6)**
GASTROINTESTINAL						
Nausea	2	0.7	0	0.0	**66**	**(23.4)**
Pain (abdominal)	1	0.4	1	0.4	**24**	**(8.5)**
Diarrhea	1	0.4	0	0.0	**23**	**(8.2)**
Vomiting	1	0.4	0	0.0	**31**	**(11.0)**
MUSCULO-SKELETAL						
Arthralgias	1	0.4	0	0.0	**21**	**(7.4)**
Pain (back)	3	1.1	0	0.0	**20**	**(7.1)**
Myalgia -- no Gr. 3 or 4 AE's					**20**	**(7.1)**
SKIN-APPENDAGES						
Urticaria	3	1.1	0	0.0	**22**	**(7.8)**
Pruritis	1	0.4	0	0.0	**36**	**(12.8)**
Rash	1	0.4	0	0.0	**32**	**(11.3)**
INFECTIOUS DISEASE						
Infections	1	0.4	0	0.0	**7**	**(2.5)**
Sinusitis	1	0.4	0	0.0	**16**	**(5.7)**
Herpes simplex	1	0.4	0	0.0	**12**	**(4.3)**

The per-patient frequency and severity of adverse events, according infusion number are provided in the table below. The percentage of patients experiencing any adverse event (80% vs. 40%) and the percentage of patients experiencing grade 3 and 4 toxicity (7% vs. 3%) was higher during the first infusion as compared to the second or subsequent infusion. In addition, more subjects discontinued treatment due to adverse events associated with the first infusion as compared to the second or subsequent infusions.

Integrated Safety Summary: Incidence of Adverse Events (by Patient) According to Infusion Number (n= 282)

Infusion #	# of pts	Grade of toxicity				
		Grade 1	Grade 2	Grade 3	Grade 4	Any
First	281	96	111	16	3	226 (80%)
Second	259	65	37	7	0	109 (42%)
Third	258	63	25	3	2	93 (36%)
Fourth	257	66	28	10	0	104 (40%)
Fifth/Sixth	29	0	0	0	0	0
Seventh/ Eighth	28	0	0	0	0	0
Any	281	70	132	53	13	268 (95%)
Unknown	2	56	33	4	1	97¶
Late †	281	47	51	24	8	132 (47%)§

¶ Includes 3 adverse events in which toxicity grade is unknown

§ Includes 2 adverse events in which toxicity grade is unknown

† Late toxicity includes all grade 3, 4 or serious adverse events and any event identified as possibly- or probably-related to study drug occurring >30 days but within 1 year of last adminstration of study drug

Infections were primarily Grade 1 or 2 (88% of events). The sponsor has identified seven events Grade 3 infections in six patients, none of whom were neutropenic at the time of infection. There were no Grade 4 infectious events reported. Review by FDA has identified 16 patients with 17 grade 3 infectious events. These include seven infections identified in 7 patients during the treatment period (sinusitis [n=2], pneumonia, Listeria sepsis, polymicrobial sepsis related to a central venous catheter, gastroenteritis, and reactivation of Herpes simplex), nine infectious events in eight patients (pneumonia [n=4], sepsis, upper respiratory tract infection [patient required hospitalization], myofascial infection, Herpes simplex [n=2]), and reactivation of Herpes zoster, three months after therapy, in one subject. All patients recovered with the exception of the individual with recurrent H. zoster, in whom permanent disability resulted. required antibiotic therapy and recovered.

IV. Review of the follow-up commitment

The follow-up commitments include the following:

- Additional information regarding the effects of Rituximab therapy on serum titers in previously vaccinated patients with cancer and in normal controls.
- A proposal for evaluation of the ability of subjects to respond to initial and booster vaccinations during the post-treatment period for the patients with lymphoma.

V. Results of follow-up

IDEC representatives sent in an amendment answering to the commitments mentioned above; this amendment (received 14-Oct-97) included a new protocol. The new protocol entitled "Pilot study to compare and evaluate the safety and impact of IDEC-C2B8 (IDEC-102) on immunization potential" is Protocol 102-09. The IDEC representatives were contacted on November 24th, 1997 and via teleconference agreed to the following:

- Reviewing patients' sera samples for baseline (pre-treatment) titers to antigens in two groups of patients: Normal volunteers and patients with NHL.
- To evaluate for fluctuations of the titers over time during and post-treatment.
- To evaluate for an adjuvant effect.
- To check-up on patients' titers after the 2nd immunization sooner than the original time of 9-15 months.

VI. Conclusions/comments

Since treatment of NHL does not result in improved survival, the goal of therapy in this setting is palliative. Therefore, treatment is usually initiated for control of progressive disease, marrow invasion affecting blood counts, symptomatic bulky nodal disease, B symptoms, or disease that threatens critical organs. The available treatment options may be accompanied by significant toxicity. IDEC-C2B8 represents a form of treatment with a novel mechanism of action and favorable toxicity profile. IDEC-C2B8 is given on an outpatient basis and the treatment period is brief (completed in 22 days). Durable clinical responses of greater than 6 months in approximately 50% of the subjects were observed in the two studies submitted. This was associated with improvement in tumor-related symptoms in 27 of 39 (69%) symptomatic patients. Factors ordinarily correlated with poorer response rates and shorter response durations did not appear to hold with this novel agent; the exceptions to this were evidence of marrow involvement, bulky disease, and refractoriness to previous therapy, all of which correlated with lower responses to IDEC-C2B8. One novel finding was the significant variance in response of IWF A vs. the follicular subtypes of NHL. Whether this is due to factors which might be more common in IWF A, e.g., low levels of circulating malignant cells or presence of marrow involvement, or to other, as yet unidentified factors, should be further evaluated.

Therapy was generally well tolerated. The toxicity profile, while tolerable by general standards for antineoplastic therapy, includes some toxicities in which further evaluation may assist in safer drug administration. These include the cardiovascular and hemodynamic toxicites (hypotension, arrythmias, and bradycardia), hypersensitivity-type reactions (as manifested by

angioedema, bronchospasm, laryngismus, urticaria, and hypotension), and prolonged, sustained lymphopenia.

The toxicity profile and pharmacokinetic profile both suggest a patient or disease-drug interaction, in that the profile for each is different for the first as opposed to subsequent doses. This pharmacokinetic interactions between volume of disease and tumor response should be further investigated to determine if a pharmacologically-driven treatment schedule might result in better clinical responses. Prospectively designed studies should also be considered to provide confirmation of patient- or disease-related factors which are predictive of response.

APPENDICES: LOCATIONS OF THE TRIALS

Site #	Site (**PROTOCOL 102-05**)	Location	Date approved
01	Ottawa General Hospital	Ottawa, Ontario, CANADA	June 1, 1995
03	Toronto-Sunnybrook	Toronto, Ontario, CANADA	April 11, 1995
05	University of Rochester	Rochester, NY	May 9, 1995
06	Roswell Park	Buffulo, NY	April 11, 1995
07	University of Maryland	Baltimore, MD	April 7, 1995
08	University of Virginia	Charlottesville, VA	February 14,1995
09	Fox Chase Cancer Center	Philadelphia, PA	February 28, 1995
10	University of Kentucky	Lexington, KY	April 25, 1995
11	University of Iowa	Iowa City, IA	April 20, 1995
12	Rocky Mountain	Denver, CO	March 15, 1995
13	University of Texas	San Antonio, TX	May 25, 1995
14	M.D. Anderson	Houston, TX	May 15, 1995
15	Fred Hutchinson	Seattle, WA	July 27, 1995
16	Hoag Hospital	Newport Beach, CA	March 24, 1995
17	UCSD	La Jolla, CA	April 6, 1995
18	City of Hope	Duarte, CA	May 17, 1995
19	Scripps Hospital	La Jolla, CA	March 8, 1995
20	Stanford University	Stanford, CA	May 2, 1995
21	SDRCC/Sharp Hospital	San Diego, CA	May 17, 1995
22	University of Pittsburgh	Pittsburgh, PA	June 14, 1995
25	Lombardi Cancer Center	Washington, D.C.	June 15, 1995
27	St. Louis University	St. Louis, MO	May 16, 1995
29	Michigan State University	East Lansing, MI	July 27, 1995
31	UCSF	San Francisco, CA	October 4, 1995
32	Kaiser Permanente	Vallejo, CA	July 18, 1995
33	Sutter Cancer Center	Sacramento, CA	September 13, 1995
34	Northwestern University	Chicago, IL	December 1, 1995
35	University of Arkansas	Little Rock, AR	November 21, 1995
37	West Clinic	Memphis, TN	January 17, 1995
40	Louisiana State University	Shreveport, LA	November 27, 1995
41	Texas Oncology	Dallas, TX	November 10, 1995

Date	**Sites (PROTOCOL 102-02)**
07/13/93	San Diego Regional Cancer Center; San Diego, CA 92121 and Grossmont Hospital; La Mesa, CA 91942
07/13/93	Scripps Memorial Hospitals; Encinitas, CA 92023
08/03/93	Stanford University Medical Center; Stanford, CA 93405
11/23/93	Fox Chase Cancer Center; Philadelphia, PA 19111
01/11/94	University of New Mexico Cancer Center; Albuquerque, NM 97131
02/02/94	Henry Ford Hospital; Detroit, MI 48202
03/04/94	Markey Cancer Center; Univ. of Kentucky Med. Center; Lexington, KY 40536

APPENDICES

Integrated Safety Summary

Incidence of Laboratory Abnormalities (Change in Grade from Baseline) by Pt. Observed During Treatment Period

Laboratory Parameter	Change in Value by Toxicity Grade			
	Grade 1	Grade 2	Grade 3	Grade 4
Anemia	44/276 (16%)	4/276 (1%)	1/276 (<1%)	0
Leukopenia	86/276 (31%)	19/276 (7%)	0	0
Neutropenia	55/273 (20%)	18/273 (7%)	2/273 (<1%)	2/273 (<1%)
Platelet count	9/276 (3%)	4/276 (1%)	1/276 (<1%)	0
Lymphopenia	90/274 (33%)	27/274 (10%)	7/274 (3%)	2/274 (<1%)
Increased creatinine	8/273 (3%)	1/273 (<1%)	0	0
Increased SGOT	16/270 (6%)	2/270 (<1%)	0	0
Increased SGPT	8/249 (3%)	0	0	0
Increased Alk. Phosphatase	10/274 (4%)	1/274 (<1%)	0	0
Increased total bilirubin	1/273 (<1%)	7/273 (3%)	1/273 (<1%)	1/273 (<1%)

Incidence of Laboratory Abnormalities (Change in Grade from Baseline) by Pt. Observed During Follow-up Period

Laboratory Parameter	Toxicity Grade			
	Grade 1	Grade 2	Grade 3	Grade 4
Anemia	13/231 (6%)	2/231 (<1%)	1/231 (<1%)	0
Leukopenia	45/231 (19%)	16/231 (7%)	5/231 (2%)	0
Neutropenia	22/226 (10%)	15/273 (7%)	2/273 (<1%)	2/273 (<1%)
Platelet count	9/276 (3%)	4/276 (1%)	1/276 (<1%)	0
Lymphopenia	90/274 (33%)	27/274 (10%)	7/274 (3%)	2/274 (<1%)
Increased creatinine	8/273 (3%)	1/273 (<1%)	0	0
Increased SGOT	16/270 (6%)	2/270 (<1%)	0	0
Increased SGPT	8/249 (3%)	0	0	0
Increased Alk. Phosphatase	10/274 (4%)	1/274 (<1%)	0	0
Increased total bilirubin	1/273 (<1%)	7/273 (3%)	1/273 (<1%)	1/273 (<1%)

Protocol 102-05

Adverse Events* During the *Treatment Period* by Body System and Grade in 166 Patients

Body System	Severity grade (Number of subjects reporting events)				All severity grades	
	grade 1	grade 2	grade 3	grade 4	# pts (%)	# events (%)
	57	74	15	3	149 (%)	840 ( )
Body As A Whole						
Fever	30	46	0	0	76(46%)	92 (8%)
Chills	26	20	3	0	49(30%)	56 (5%)
Headache	19	7	2	0	28(17%)	33 (3%)
Asthenia	19	7	1	0	27(16%)	32 (3%)
Pain	10	3	0	0	13 (8%)	15 (1%)
Abdominal Pain	6	5	0	0	11 (7%)	15 (1%)
Back Pain	5	2	2	0	9 (5%)	9 (<1%)
Flushing	4	1	0	0	5 (3%)	6 (<1%)
Cardiovascular System						
Hypotension	8	7	1	0	16 (10%)	19 (2%)
Arrhythmia	3	0	1	1	5 (3%)	9 (<1%)
Digestive System						
Nausea	27	11	2	0	40 (24%)	49 (4%)
Vomiting	11	9	1	0	21 (13%)	22 (2%)
Diarrhea	13	3	1	0	17 (10%)	21 (2%)
Hemic And Lymphatic System						
Leukopenia	7	3	2	0	12 (7%)	14 (1%)
Neutropenia	2	5	0	1	8 (5%)	10 (<1%)
Thrombocytopenia	6	1	1	0	8 (5%)	9 (<1%)
Anemia	0	1	3	0	4 (2%)	4 (<1%)
Metabolic And Nutritional Disorders						
Angioedema	18	6	1	0	25(15%);	32 (3%)
Hyperglycemia	9	1	0	0	10 (6%);	10 (<1%)
Peripheral edema	2	2	0	0	4 (2%)	4 (<1%)

Protocol 102-05
Adverse Events* During the *Treatment Period* Classified by Body System and by Grade (n=166 Patients)
(continued)

Musculoskeletal System						
Myalgia	4	8	0	0	12 (7%)	12 (1%)
Arthralgia	6	5	0	0	11 (7%)	13 (1%)
Pain	1	2	1	0	4 (2%)	4 (<1%)
Hypertonia	2	0	1	0	3 (2%)	3 (<1%)
Nervous System						
Dizziness	10	2	0	0	12 (7%)	13 (1%)
Flushing	**3**	**1**	**0**	**0**	**4 (2%)**	**4 (<1%)**
Respiratory System						
Rhinitis	14	3	1	0	18(11%)	21 (2%)
Bronchospasm	12	4	1	0	17(10%)	19 (2%)
Cough Increase	5	5	1	0	11 (7%)	11 (<1%)
Dyspnea	1	1	1	0	3 (2%)	3 (<1%)
Skin And Appendages						
Pruritus	19	2	1	0	22(13%)	23 (2%)
Rash	14	3	0	0	17(10%)	17 (2%)
Urticaria	8	3	1	0	12 (7%)	12 (1%)
Night Sweats	4	2	0	0	6 (4%)	6 (<1%)
Pain	1	0	1	0	2 (1%)	2 (<1%)
Skin Carcinoma	0	0	1	0	1 (<1%)	1 (<1%)
Infections						
Sinusitis	5	3	1	0	9 (5%)	9 (<1%)
Pharyngitis	6	2	0	0	8 (5%)	9 (<15)
Infection, Respiratory	3	3	0	0	6 (4%)	6 (<1%)
Infection	1	1	1	0	3 (2%)	4 (<1%)
Herpes Simplex	3	3	0	0	6 (4%)	6 (<1%)

Protocol 102-05: Serious Adverse Events Requiring Hospitalization							
Patient #	**Study day**	**Adverse event**	**Grade**	**Attribution to C2B8**	**Effect on dosing**	**Treatment intervention**	**Outcome**
008	32	abdominal pain	N/A	Other	none	Hospitalized	Improved
017	50	pneumonia	2	possibly	none	Hospitalized	Recovered
	174	acute retinal necrosis	3	possibly	none	Hospitalized	Recovered
018	15	Listeria infection	2	unknown	Interrupted*	Hospitalized	Recovered
022	3	headache	3	concurr illness	none	Hospitalized	Recovered
	3	simusitis	3	concurr illness	none	Hospitalized	Recovered
023	53	sinusitis	2	concurr illness	none	Hospitalized	Recovered
028	1	angioedema	3	possibly	discontinued	Hospitalized	Recovered
	1	dyspnea	3	possibly	discontinued	Hospitalized	Recovered
	1	rhinitis	3	possibly	discontinued	Hospitalized	Recovered
029	166	bone fracture	3	none	other	Hospitalized	Ongoing
036	186	myofascial infection	3	possibly	none	Hospitalized	Recovered
044	164	congestive heart failure	4	unknown	none	Hospitalized	Controlled
046	79	aplastic anemia	3	possibly	none	Hospitalized	Controlled
	150	Herpes simplex	3	concomm drug	none	Hospitalized	Recovered
050	144	heart failure	3	other	none	Hospitalized	Controlled
	144	myocardial infarction	3	other	none	Hospitalized	Recovered
	147	bilateral pneumonia	2	possibly	none	Hospitalized	Recovered
060	56	abdominal pain	2	concurr illness	none	Hospitalized	Recovered
061	1	bronchospasm	3	probably	discontinued	Hospitalized	Controlled
		chills	3	probably	discontinued	Hospitalized	Controlled
		cough increase	3	probably	discontinued	Hospitalized	Controlled
		nausea/vomiting	3	probably	discontinued	Hospitalized	Controlled
065	51	dyspnea	2	concurr illness	none	Hospitalized	Recovered
	108	pneumonia	2	concurr illness	none	Hospitalized	Recovered
074	120	upper respiratory infection	N/A	other	none	Hospitalized	Resolved
088	13	left hip pain	2	other	none	Hospitalized	Recovered

Protocol 102-05: Serious Adverse Events Requiring Hospitalization (Continued)							
Patient #	**Study day**	**Adverse event**	**Grade**	**Attribution to C2B8**	**Effect on dosing**	**Treatment intervention**	**Outcome**
092	15	arrhythmia	4	possibly	discontinued	Hospitalized	Recovered
094	242	anemia	N/A	other	none	Hospitalized	Improved
		fever	N/A	other	none	Hospitalized	Improved
		cough	N/A	other	none	Hospitalized	Improved
099	91	pneumonia	3	possibly	none	Hospitalized	Recovered
109	188	abdominal pain	3	concurr illness	none	Hospitalized	Controlled
	193	nausea/vomiting	2	concurr illness	none	Hospitalized	Recovered
		abdominal pain	3	concurr illness	none	Hospitalized	Ongoing
	240	abdominal pain	N/A	other	none	Hospitalized	Improved
	245	abdominal pain	N/A	other	none	Hospitalized	Improved
118	1	hypotension	3	possibly	discontinued	Hospitalized	Improved
124	210	pneumonia	N/A	possibly	none	Hospitalized	Resolved
138	22	hydronephrosis	N/A	other	none	Hospitalized	Ongoing
140	1	chills	1	possibly	none	Hospitalized	Recovered
		fever	2	possibly	none	Hospitalized	Recovered
	26	diarrhea	3	other	none	Hospitalized	Recovered
		fever	2	other	none	Hospitalized	Recovered
		nausea	3	other	none	Hospitalized	Recovered
	27	gastroenteritis	2	unknown	none	Hospitalized	Recovered
153	22	Squamous cell CA	3	concurr illness	none	Other	Recovered
155	42	chills	2	other	none	Hospitalized	Recovered
		infection	3	other	none	Hospitalized	Recovered
157	8	fever	2	probably	none	Hospitalized	Recovered
	21	cough increase	2	probably	none	Hospitalized	Recovered